

**REMARKS**

Claims 2, 4, 39 and 40 have been amended herein. Claims 1-5, 8-27 and 37-41, including independent claims 1, 37, 39 and 40, are thus pending for reexamination and reconsideration, which are respectfully requested in view of the foregoing amendments and following remarks.

In the August 1, 2003, office action, claims 1-5, 7-11, 13-17, 26-27, 37-38 and 41 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Johnson. Claims 1-5, 7, 10-11, 13-27 and 37-38 were rejected under 35 U.S.C. 103(a) as obvious over Johnson in view of Jenkins, Knappik, Dubel and Kostelny. Claims 1-5 and 13-27 were rejected under 35 USC § 112, second paragraph, as indefinite. Claim 27 was rejected under 35 USC § 101 as being directed to non-statutory subject matter. Claims 1-2, 4-5, 8-9, 12-13, and 26-27 were rejected under 35 USC § 102(e) as anticipated by Stevens. Claims 1-5, 8-27, 37-38 and 4 were rejected as obvious over Stevens in view of Jenkins, Knappik, Dubel and Kostelny.

**Rejections under § 101**

Claim 27 stands rejected under 35 USC § 101 as being directed to non-statutory subject matter. Specifically, the Examiner alleges that the host cell recited in claim 27 is not distinguished over naturally occurring cells. Applicants respectfully traverse the rejection. Claim 27 recites a host cell encoding a vector that encodes a modified antibody. Modified antibodies do not occur in nature. Accordingly, host cells expressing such modified antibodies also do not occur in nature and withdrawal of the rejection respectfully is requested.

**Rejections under § 102(b)**

Claims 1-5, 7-11, 13-17, 26-27, 37-38 and 41 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Johnson. Specifically, the Examiner alleges that the instantly claimed modifications are taught by Johnson. Applicants respectfully traverse.

The present invention claims amino acid modifications to a variable domain that stabilize the inter domain interface, where the modified domain is capable of interacting with a second variable domain to form a functional antibody molecule or fragment. These modifications are quite distinct from the modifications described by Johnson, which are directed solely to modifications that are intended to stabilize so-called "domain antibodies" (single heavy domain

molecules). Johnson's domain antibodies, by definition, are not intended to interact with a second variable domain to form a functional antigen binding molecule, but rather are intended to bind antigen without a second variable domain. There is no evidence in Johnson that the modified domain antibody can productively interact with a second variable domain to form a functional antibody or fragment. Accordingly, Johnson does not teach each and every limitation of the claimed invention and the rejection should be withdrawn

#### **Rejections under § 102(e)**

Claims 1-2, 4-5, 8-9, 12-13, and 26-27 are rejected under 35 USC § 102(e) as anticipated by Stevens. Specifically, the Examiner alleges that Stevens teaches modifications of the inter-domain interface that increase the hydrophilicity of an antibody or antibody fragment. Applicants respectfully traverse.

Stevens teaches a single substitution at position 38 (corresponding to position 46 in the numbering scheme of the instant application) in single variable light chains, with the intention of promoting formation of light chain-light chain dimmers. See column 9 generally. Accordingly, modification of Steven's antibody domain is intended to promote interaction with the *same* modified domain. Indeed, the modification proposed by Stevens is intended to impair or prevent binding of the modified light chain with a second (heavy) chain.

By contrast, the modified molecules recited in the instant claims are fully capable of interacting with a *second* variable domain to form a functional antibody molecule or fragment. Stevens fails to describe such a modified antibody that is capable of interacting with a second variable domain to form a functional antibody molecule or fragment. Accordingly, Stevens fails to teach each and every limitation of the claimed invention and the rejection should be withdrawn.

#### **Rejections under § 103(a)**

Claims 1-5, 7, 10-11, 13-27 and 37-38 are rejected under 35 U.S.C. 103(a) as obvious over Johnson in view of Jenkins, Knappik, Dubel and Kostelny. Claims 1-5, 8-27, 37-38 and 4 are rejected as obvious over Stevens in view of Jenkins, Knappik, Dubel and Kostelny. Applicants respectfully traverse.

For the reasons described above, Johnson fails to teach or suggest functional antibody formats that contain a first variable domain capable of interacting with a second variable domain to form a functional antibody molecule or functional fragment thereof. Instead, Johnson narrowly suggests the modification of amino acids at the portion of a "single variable domain" that otherwise would interact with its variable domain complement, and Johnson specifically sanctions the making of these modifications in order to inhibit this interaction. Johnson, therefore, teaches directly away from applicants' claimed invention. See In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983).

Similarly, Stevens allegedly describes a method of modifying a light chain to promote self-dimerization and fails to teach or suggest functional antibody formats that contain a first variable domain capable of interacting with a second variable domain to form a functional antibody molecule or functional fragment thereof. Accordingly, Stephens like Johnson, teaches away from the instantly claimed invention.

None of the secondary references make up for the deficiencies of Johnson or Stevens, or would have suggested to one of ordinary skill in the art that modifying the teachings of Johnson or Stevens would somehow lead to the claimed invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 103(a).

#### **Rejections under § 112, second paragraph**

Claims 1-5 and 13-27 are rejected under 35 USC § 112, second paragraph, as indefinite. Specifically, the Examiner alleges that various terms in the claims are undefined and/or unclear. Applicants address the rejections in the order set forth in the office action.

First the Examiner queries the meaning of the term "functional fragment." Applicants point to page 16, lines 8-9 of the instant specification which states that "[t]he functionality of the scFv was tested by competition ELISA." This indicates that in the context of the present invention, the term functional refers, at a minimum, to the ability to bind a target molecule. This is a conventional meaning that is well understood in the art. Accordingly, applicants respectfully submit that the term is definite and request withdrawal of the rejection.

Second, with reference to the term "capable of interacting," the Examiner asks "[d]oes the first variable domain interact with a second variable domain or not?" Applicants respectfully submit that the claims at issue are composition claims and that claim elements that refer to

binding steps of the type queried by the examiner are more appropriately recited in method claims. The claims as presently formulated specify that the modified domain *can* bind to a second domain to form a functional antibody fragment, which is a property inherent in the structure of the modified antibody. This inherent property of the modified domain is well understood in the art which is all that § 112, second paragraph requires. Accordingly, withdrawal of the rejection is requested.

With respect to the rejection of claims 2 and 4, applicants submit that these rejections are moot in light of the foregoing amendments to the claims.

With respect to the rejection of claim 17, applicants respectfully submit that the surface protein is recited in claim 15, from which claim 16 ultimately depends.

With respect to the rejection of claims 39 and 40 for the recitation "former interface" applicants submit that these rejections are moot in light of the foregoing amendments to the claims. With respect to the term "said modification," applicants respectfully submit that the claims refer to a "modified" interface and that "said modification" refers to the change that produced the modified interface. As such, the claim fully complies with § 112, second paragraph, and withdrawal of the rejection is requested.

**Conclusion:**

In view of the foregoing, applicants respectfully submit that the case is in condition for allowance. The Examiner is invited to contact the undersigned attorney to resolve any issues, in order to expedite the prosecution of the application.

Respectfully submitted,



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Date

Paul M. Booth  
Reg. No. 40,244

Customer ID No. 26633  
HELLER EHRMAN WHITE & McAULIFFE  
1666 K Street, NW, Suite 300  
Washington, DC 20006-1228  
(202) 912-2000 (telephone)  
(202) 912-2020 (telecopier)